The Interplay between COVID-19 and Cancer: Challenges and Perspectives

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Introduction

We are now nearly 2 years into the coronavirus disease 2019 (COVID-19) pandemic. As we learn to exist and move ahead, embracing the "new normal" with COVID-19, both at a professional and personal level, it is time to reflect on some of the challenges and lessons from the pandemic. COVID-19, one of the most devastating health emergencies of the century, has laid bare the inefficiencies of modern health systems and led to 5 million deaths worldwide.[1] The varying case fatality rates of 0.5 to 2.5% and the absolute numbers of deaths reported from different countries are still lower than the mortality due to noncommunicable diseases and other infectious diseases.[1] This is not to belittle the devastation caused by the pandemic but to draw attention to the impact that COVID-19 and the response to the pandemic have had on systems needed for prevention and management of these other illnesses. In this article, we explore the complex interplay between cancer and COVID-19, the impact of cancer on COVID-19 severity and outcomes, and how COVID-19 affected several levels of care in the diagnosis and management of cancer.

Cancer Burden in India and Other Low- and Middle-Income Countries

It is important to have a perspective on the burden of cancer and the challenges which are faced by patients, their families, oncologists, and institutions in our country and other low- and middle-income countries (LMICs) even prior to the pandemic. As per GLOBOCAN data, the global incidence of all cancers is 19 million cases annually with nearly 10 million deaths per year.[2] Though the overall incidence of cancer is more in high-income countries, LMICs account for nearly two-thirds of cancer deaths.[2] This high mortality-to-incidence ratio is largely due to delayed diagnosis, late-stage presentation, inadequate access to care, and unaffordability of treatment.[3] Cancer care is limited to the larger cities with wide variations in infrastructure and expertise between centers. Access to cancer care requires considerable amount of travel, long stays away from home, loss of wages, and significant out-of-pocket expenditure that unfortunately results in high rates of treatment abandonment. Another important issue is the poor distribution of palliative care services and access to opioids which result in poor quality of life in advanced-stage cancers.

COVID-19 in Patients with Cancer

Cancer has been identified as a risk factor for severe COVID-19 and poor outcomes after COVID-19. During the course of pandemic, several studies evaluated the possible risk factors for adverse outcomes in patients with COVID-19 and cancer —these included advanced age, multiple comorbidities, smoking, hematological cancers, and the use of systemic anticancer therapy.[4] Patients with cancer who developed COVID-19 have been reported to have fatality rates between 10 and 30%.[5–11] As data emerged on the high risk of developing COVID-19 and its complications in patients with cancer, most professional bodies advised delays or modification of intensive treatment, including postponement of elective surgeries and hypofractionation of radiation therapy.[12]

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COVID-19 in India

As on November 11, 2021, India has seen nearly 35 million cases of COVID-19.[1] The overall case fatality has been 1.3%, which is considerably lower than in many other countries.[1] This difference in outcomes has been attributed to several reasons: underreporting of cases, unreliable death certification, and possible cross-immunity due to previous coronavirus infection.[13,14] There are very little data from India on the outcomes of patients with both cancer and COVID-19. Mehta et al reported a 14.5% case fatality rate, with presence of comorbidities being the only significant risk factor for mortality.[15] Recent systemic cancer therapy had no impact on COVID-19 outcomes. Ramaswamy et al looked at 236 patients with cancer on active therapy; the all-cause mortality rate was 10%. Independent predictors of mortality were advanced-stage cancer treated with palliative intent, severe COVID-19, and uncontrolled cancer status.[16] Radhakrishnan et al reported on COVID-19 in 15 pediatric patients with cancer, all of whom had an uneventful recovery.[17] Unpublished data from our center evaluating 1,253 patients with cancer found that the majority of them (90%) had mild COVID-19, and the mortality rate was around 10%. The type of cancer and systemic anticancer therapy in last 30 days prior to COVID-19 diagnosis did not increase mortality, except in patients with advanced age who were being treated with palliative intent. This suggests that at least in India, most patients with cancer who develop COVID-19 have a favorable prognosis, and their cancer treatment should continue without interruption. The data from children with cancers are more reassuring. Most patients develop asymptomatic to mild infections, and continuation of treatment in these patients does not result in excess mortality.[18,19]

Impact of COVID-19 on Cancer Care

The impact of COVID-19 on cancer care has been more widespread and substantial. A systematic review by Riera et al included 62 studies across 15 countries reporting substantial disruptions and delays in cancer services during the pandemic.[20] In India, multiple factors may have contributed to this. First, due to travel restrictions during the national lockdown, and fear of travel during the pandemic, many patients were unable to access cancer centers. Second, resources and manpower available for cancer care were diminished for a multitude of reasons—reallocation of oncology beds and health care workforce to facilitate COVID-19 management, travel restrictions preventing staff from reaching the work place, staff-sparing strategies to minimize the risk of infection, and infections or quarantine among staff. Third, most cancer centers suspended their cancer prevention and screening programs due to the risk of infection, and the need to divert staff and resources for COVID-19 management. The national cancer screening program in India was also put on hold since May 2020.[21] Data from 41 cancer centers across the country showed that during the peak of the pandemic (March–May 2020), there was a reduction by two-third in most cancer services, whereas screening activities were almost at a standstill.[22] These reductions were across new patient registrations, follow-up visits, major and minor surgeries, day care chemotherapy, diagnostic testing, and palliative care referrals. The number of patients accessing radiotherapy services showed the least reduction (23%).[22] These factors may have possibly led to stage migration and increased mortality due to delays in diagnosis and treatment, and interruptions in ongoing treatments. Even among patients who sought and received cancer care, modifications and deintensification of treatment regimens could have resulted in compromised outcomes, more so in the curative setting. Similarly, interruption of palliative care services and access to opioids, which were already limited across the country, posed challenges in the care of advanced cancers.

A systematic review has estimated that even a 4-week delay of cancer treatment is associated with increased mortality across surgical, systemic treatment, and radiotherapy indications for seven cancers.[23] While there are no data from India to quantify the impact of the disruptions in care due to COVID-19, several global studies have used modeling techniques to estimate the likely consequences. Maringe et al predicted that in England, there would be 3,620 avoidable cancer deaths in the next 5 years for four major cancers (breast, bowel, lung, and esophageal) representing ~40% of total burden.[24] These additional excess cancer deaths would amount to a loss of 32,700 quality-adjusted life years and productivity losses of 103.8 million British pounds in the next 5 years.[25] Rutter et al reported a 58% decrease in cancer detection during the peak of the pandemic due to reductions in endoscopy services in the United Kingdom.[26] Sud et al reported between 3,316 and 9,948 additional life years lost due to delays in referral during the 3-month lockdown period in the United Kingdom.[27] Data from Australia estimate at a conservative level, 88 additional deaths and 12 million Australian dollars spent in excess health care costs over 5 years for all patients diagnosed in 2020.[28] These numbers are staggering and reflect the profound impact that the pandemic is likely to have on oncological outcomes in the next few years.

Cancer education has also been badly affected during the pandemic, with compromised training in specialty areas due to involvement in COVID-19 care.[22] Reduced numbers of patients visiting cancer centers have resulted in trainees receiving suboptimal exposure to various aspects of cancer management. Research in oncology has been put on the backburner due to diversion of research staff to COVID-19 care, reluctance of research participants to make nonessential hospital visits, global recommendations to avoid intensive research interventions, and cuts in research funding.[22] As a result, several oncology research studies have reported protocol violations, setbacks in initiation and accrual, and likely delays in study completion and analysis, thereby postponing the availability of the results.

The treatment of COVID-19 has evolved over time. Keeping in mind the underlying pathophysiology of cytokine storm and activation of downstream pathways, several clinical trials evaluated the repurposing of some anticancer

drugs such as imatinib, bruton tyrosine kinase (BTK) inhibitors, and Janus kinase/Signal transducers and activators of transcription (JAK-STAT) pathway inhibitors.[29] One of the underlying pathophysiological mechanisms responsible for several of the sequelae of COVID-19 is vascular thrombosis. Patients with cancers have a high risk of thromboembolic events. Infection with COVID-19 may further amplify this risk, warranting prophylactic anticoagulation, based on the underlying factors. Treatment of moderate to severe COVID-19 with dexamethasone and tocilizumab can have potential adverse outcomes in those with concomitant neutropenic sepsis warranting a careful decision and close monitoring.

Vaccination is the only long-term measure to gain control over the COVID-19 pandemic. However, patients with cancer faced several hurdles for vaccination. Paradoxically, limited data on the safety and efficacy of the vaccine in this category of patients led to a delayed start of the vaccination process in the population which possibly needed it the most. For patients with cancer on active cancer therapy, there was an initial lack of clarity on eligibility criteria to receive the vaccine. Finally, it is known that immunosuppressed patients may not have a robust serological response to the vaccine, suggesting the need for booster doses, in a situation where vaccines are already in short supply.

An important area which has been inadequately focused on during the pandemic is mental health.[30] Patients who have been quarantined or isolated during the pandemic have experienced feelings of anxiety and depression. In addition, several health care workers have faced emotional burnout due to the psychological burden of loss, fear of getting infected, long working hours, difficulty due to continuous use of PPE, social stigma among family and neighbors, and problems with staying away from their families after caring for patients with COVID-19.[31]

It is now known that patients who recover from COVID-19 may continue to have persistent debilitating symptoms for several months after the initial infection, known as "post-COVID-19 syndrome" or "long COVID-19." The World Health Organization defines post-COVID-19 condition as "occurring in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis."[32] Some systems further classify post-COVID-19 into subacute (lasting 4–12 weeks after the initial diagnosis) and chronic (lasting beyond 12 weeks) conditions. The manifestations of post-COVID-19 syndrome include fatigue, sleep disturbances, cognitive dysfunction, respiratory symptoms with a restrictive pattern of lung disease, myocarditis, and endothelial dysfunction, among many others. Pinato et al found that 15% of patients with cancer who developed COVID-19 had post-COVID-19 sequelae, leading to treatment modifications and discontinuations in a significant proportion.[33] Permanent treatment discontinuation was an independent risk factor for mortality. Cancer centers are now seeing increasing numbers of patients who have recovered from COVID-19 and presenting for management of their cancer. It is essential to recognize the implications of the previous COVID-19 infection, advise appropriate evaluation and risk stratification, before proceeding with cancer therapy. There are several recommendations for the evaluation of COVID-19 survivors to identify sequelae of COVID-19 prior to initiating other therapies.[34–37] Recognition of the sequelae of COVID-19 is especially important while using systemic anticancer therapy with potential cardiac, pulmonary, hepatic, or renal toxicity, and would warrant appropriate assessment and close monitoring. Mucormycoses emerged as another threat in patients who had severe COVID-19. The use of steroids, environmental factors, poorly controlled blood sugar, and oxygen sources were implicated for this outbreak. Mucormycosis has been a known enemy for patients with hematological cancers who are treated with steroids and have underlying diabetes mellitus.[38] This makes it essential to monitor such patients who develop COVID-19 and maintain stringent blood sugar control along with judicious use of steroids.

Lessons from the Pandemic

Amidst this picture of gloom, the pandemic has taught us several lessons and had many positive outcomes. To circumvent the problems with access to cancer care, most centers started the facility of teleconsultation enabling the continued delivery of care and minimizing the need for in-person visits. The widespread acceptance and success of these teleconsultations suggest that even in future, remote consultation should be adopted wherever feasible. This can have remarkable benefit in reducing the need for follow-up visits. This also has the potential to decentralize medical care with optimal resource utilization using the "hub and spoke" model. The delivery of oral drugs through courier facilitated the continuation of treatment, both for routine care and for patients on research protocols—an ideal practice that should be continued even postpandemic. COVID-19 resulted in the setting up of isolation wards and adoption of better infection control practices. Several studies have reported reductions in hospital infections as a result of these measures. These practices can help reducing the transmission of multidrug-resistant organisms, a major threat in immunocompromised patients with cancer.[39] Most centers ramped up their testing services during the pandemic. This investment in infrastructure and manpower will be useful in the coming years, for other infectious diseases as well as molecular diagnostics of cancer. The pandemic resulted in several drugs being tested as a cure for COVID-19, with the establishment of multicentric collaborations, development of pragmatic protocols, and initiation of research studies within rapid timelines. The establishment of collaborative registries led to a better understanding of the impact and outcomes of COVID-19 in patients with cancer.[40] Simultaneously, there were modifications in ethics committee processes to facilitate new and ongoing research via adoption of telephonic consent, expedited and virtual reviews, remote monitoring, drug delivery directly to the patient, and pragmatic response assessment timelines.[41] All of these processes have shown us more efficient ways of conducting research. Research studies such as the "RECOVERY" and "SOLIDARITY" trials are leading

examples of pragmatic clinical trials which have shown wide external validity, with a variety of populations and settings, and the ability to accrue rapidly with minimal burden on the existing infrastructure at research sites. Oncology trials can learn from these studies to ensure better generalizability of their results.[42,43]

Educational activities shifted largely to the online format, enabling several who could not have attended otherwise to participate.[44] Many international teaching programs and course materials were made accessible to all. The use of simulation techniques to replace actual clinical experience has gained popularity. These changes can be incorporated into future academic activities which can be blended or hybrid (virtual and in-person), thereby increasing their scope and reach. Another blessing in disguise has been the reduction in the carbon footprint generated by the decrease in travel for meetings and conferences. The recognition of mental health challenges during the pandemic and the establishment of support services for those with psychological issues are a huge step forward.

Summary

COVID-19 has had a substantial impact on various aspects of cancer care, both through the direct effects of the infection, via its repercussions on cancer management, and the cancer care workforce. As we continue to find a balance between minimizing the risk of COVID-19 infection and continuing care for patients with cancer, there are several positive lessons that will stand us in good stead for the future.

Conflict of Interest
None declared.

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